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META-ANALYSIS

Helicobacter pylori infection and asthma: Is there a direct or an inverse association? A meta-analysis

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Abstract

AIM: To analyze the consistency of a potential involvement of the bacterium infection in the asthma disease.

METHODS: A systematic literature search of the terms "*Helicobacter pylori*" (*H. pylori*) associated to "asthma" using PubMed, Scopus and the Cochrane Library Central was performed. Reference lists from published articles were also employed. Titles of these publications and their abstracts were scanned in order to eliminate duplicates and irrelevant articles. The criteria of inclusion of the studies were: Original studies; the *H. pylori* diagnostic method has been declared; all ranges of age have been included in our study; a definitive diagnosis of asthma has been reported.

RESULTS: We selected 14 articles in which the association between the two conditions was addressed. In 7 studies the prevalence of *H. pylori* infection in the asthma population and in the control population was made explicit. There was heterogeneity between the studies (Cohran's Q = 0.02). The *H. pylori* infection in the asthma population resulted 33.6% (518 of 1542), while in the control population resulted 37.6% (2746 of 7310) (relative risk of *H. pylori* infection in the asthma population = 0.87, 95%CI: 0.72-1.05, *P* = 0.015, random effects model). Instead, considering the more

virulent strains, the majority of studies showed an inverse relationship between the prevalence of *H. pylori* infection and asthma.

CONCLUSION: In our meta-analysis the prevalence of *H. pylori* infection in the asthma population resulted not statistically significant lower than in control population (P = 0.15). Instead, considering the more virulent strains, the majority of studies showed an inverse relationship between the prevalence of *H. pylori* infection and asthma.

Key words: Allergic diseases; Asthma; Extragastric manifestations; *Helicobacter pylori*; Hygiene

Core tip: The relationship between *Helicobacter pylori* infection and asthma is an important issue, since it could influence the choice of treatment. In our meta-analysis the prevalence of the infection in the asthma population resulted not statistically significant lower than in control population.

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INTRODUCTION

Asthma is a common respiratory disease, manifested by inflammatory and obstructive processes, secondary to multiple stimuli[1].

The etiology of asthma remains largely unclear. In the latest decades the prevalence of allergic asthma increased in children[2]. The reason is unknown. Changes in personal or maternal smoking habits, types of dwelling, adaptation to Western dietary habits, less infections, as a consequence of vaccinations, decreased family size and hygiene[3], air pollution, work exposure or changed microbiota due to occidental style of life[4] might be possible causes[5]. Some infectious agents, that affect specific organs, can also cause systemic diseases. Hence, it has been postulated that infections drive the differentiation of T helper (Th) cells to the Th1 subtype with resulting suppression of the Th2 subtype, involved in IgE-mediated allergy[3,6]. However, the theory that some infections in early childhood may prevent atopic sensitization (the "hygiene hypothesis")[7] is hotly debated[8].

The *Helicobacter pylori* (*H. pylori*) is a gram-negative, spiral shape, mobile, microaerophilic bacillus[9] that we can find in all over the world[10]. The *H. pylori* infection is chronic and the humans are infected in the first 10 years of age, especially in children living in family with a low socio-economic status. In the latest two decades links between *H. pylori* infection and extragastric manifestations have been reported[11]. The diseases in which a possible role of *H. pylori* has been hypnotized are cardiovascular diseases, hepatic diseases, skin diseases, rheumatologic diseases, blood diseases, *etc*[12,13].

The present review attempts to highlight the data regarding a potential link between *H. pylori* and asthma[14].

MATERIALS AND METHODS

Literature search

PRISMA statement guidelines were followed for conducting and reporting meta-analysis data[15]. PICOS scheme was followed for reporting inclusion criteria.

A MEDLINE, Scopus and the Cochrane Library Central query "*Helicobacter pylori*" or "*Helicobacter*" and "asthma" was performed. Reference lists from published articles were also employed. Titles of these publications and their abstracts were scanned in order to eliminate duplicates and irrelevant articles. The last access was dated March 12, 2016. Articles not in English were read by a specific native speaker.

Study selection

The criteria of inclusion of the studies were: (1) original studies; (2) the *H. pylori* diagnostic method has been declared; (3) all ranges of age have been included in our study; and (4) a definitive diagnosis of asthma has been reported.

Data extraction

Two authors (Fagoonee S and Colombini J) independently reviewed the literature search results and selected relevant studies. The full-text studies were assessed by the two authors to determine whether the inclusion criteria were met[16].

Risk of bias

The quality of each study was defined on the basis of the following criteria: (1) selection of patients and controls; (2) methods used to diagnose *H. pylori* infection; (3) diagnostic method of respiratory disease; (4) type of statistical analyses performed; and (5) adjustment for confounding factors. Data abstraction and an estimate of the quality were performed independently by all the authors, who compared the results and then reached a consensus. Assessment was not blind to names and origins of the authors or publications.

A meta-analysis has been performed of the studies in which the percentage of *H. pylori* infection in the asthma population and in the control population was made explicit.

Statistical analysis

When heterogeneity was present the random effects model was preferred to the fixed effects model. Cohran's

Table 1 Association between *Helicobacter pylori* infection and Asthma in paediatric population

Ref.	Method for assessing *H. pylori* infection	Association	No. of asthmatic/ No. of control	Age	Quality
Annagür *et al*[17]	Serological	Seropositivity was similar in acute exacerbations and stable asthmatics	79/36	5-15	3/5
Zevit *et al*[18]	^{13}C-urea breath test	Inverse association between *H. pylori* and pediatric asthma	578/6381	5-18	5/5
Khamechian *et al*[19]	Biopsy samples	Inverse association between *H. pylori* and pediatric asthma	36/264	5-18	4/5
Karimi *et al*[20]	^{13}C-urea breath test	Similar prevalence in cases and controls	98/98	< 18	2/5
den Hollander *et al*[4]	Serological	Positive association between *H. pylori* CagA- and pediatric asthma	3062/0	6	3/5

H. pylori: *Helicobacter pylori*; CagA: Cytotoxin-associated gene A.

Q was used to test the heterogeneity and a P value < 0.1 was used as a cut-off for significance.

The results of the different studies, with 95%CI, and the overall effect with 95%CI, were illustrated in a forest plot graph; the pooled effects have been represented using a diamond.

A Freeman-Tukey transformation was used to calculate the weighted summary "proportion". The Mantel-Haenszel method was used for calculating the weighted pooled "relative risk". Statistical analyses were conducted using Med Calc® version 14.8.1 software. The statistical review of the study was performed by a biomedical statistician.

RESULTS

Study selection

The search identified 169 publications. We read the abstracts of all articles and selected the 14 original papers where the inclusion criteria were met.

Epidemiology of the association

Pediatric population: Five studies included children with diagnosed asthma (Table 1) and in one study was described children with wheezing but not with a clear diagnosis of asthma: (1) in a monocentric, sample size: 115 participants (79 cases), follow-up: 24 mo, case-control study (quality: 3/5) on a pediatric population, the authors found no positive correlation between IgM and IgG antibodies to *H. pylori* and acute exacerbation or stable asthma (P = 0.494 and P = 0.227 respectively)[17]; (2) in a monocentric, sample size: 6959 participants (578 cases), follow-up: 24 mo, observational study, performed using the ^{13}C-urea breath test (UBT) (quality: 5/5), an inverse association between *H. pylori* and pediatric asthma was found (OR = 0.79, 95%CI: 0.66-0.94). In this case, a diagnosis was searched in the medical records, thus minimizing familial biases[18]; (3) in a monocentric[19], sample size: 300 participants (38 cases), observational study, performed using biopsy samples (quality: 4/5), an inverse association between *H. pylori* and pediatric asthma was demonstrated (P < 0.005).

These results were not confirmed by two monocentric studies: (4) an Iranian study[20], sample size: 196 participants, follow-up: 13 mo, cross-sectional study (quality: 2/5) performed in 98 asthmatic Iranian children, that found a similar *H. pylori* prevalence in cases and controls; and (5) an European study[4], sample size: 3797, prospective (quality: 3/5) performed in 3062 children, was found an association between *H. pylori* and risk of asthma (OR = 1.75, 95%CI: 1.07-2.87); children infected by CagA- *H. pylori* strain had an increased risk of asthma (OR = 2.11, 95%CI: 1.23-3.60), while those affected by a CagA-positive strains were not (OR = 0.94, 95%CI: 0.32-2.79).

Moreover, a lower *H. pylori* infection rate in children with wheezing was found in Dutch children who participated in the allergy cohort study[21].

Adult population: Nine selected studies included adults (Table 2). All were conducted using serology to demonstrate *H. pylori* infection.

Two studies: (1) one performed in Scotland[3] (monocentric, sample size: 219 participants, 19 cases), follow-up: 360 mo, survey study) (quality: 3/5); (2) another in Hong Kong[22] (monocentric, sample size: 187 participants (90 cases), follow-up: 12 mo, observational study) (quality: 2/5), indicated that exposures to *H. pylori* was not linked with the development of asthma in adulthood; (3) in a Japanese group of hospitalized patients, Jun *et al*[14] (monocentric, sample size: 94 participants, 46 cases, follow-up: 13 mo, case-control study) (quality: 2/5) did not find difference in anti-*H. pylori* IgG seropositivity and in CagA IgG seropositivity between asthmatics and controls (socioeconomically-matched); (4) Chen *et al*[23] (follow-up: 72 mo, survey study) (quality: 3/5) included 7663 participants in which information on demographics and medical history of asthma was collected using in-person interviews and valid serologic testing for *H. pylori*. In patients infected with *H. pylori*-CagA$^+$ strains the prevalence of asthma were lower compared to uninfected subjects. Colonization by *H. pylori*-CagA$^+$ strains was inversely related to having had asthma only in patients with an age of 42 year of more younger and was also find an inverse association between childhood asthma and CagA$^+$ status; (5) similar results were found by the same authors in a following study[24] (sample size: 7412 participants, 946 cases, survey study) (quality: 3/5). They analyzed several subclasses of ages and included only subjects in the younger subclass: *H. pylori* infection seemed to be a protective factor against current or past asthma (OR = 0.49, 95%CI: 0.3-0.8); (6) another group (monocentric,

Table 2 Association between *Helicobacter pylori* infection and Asthma in adult population

Ref.	Method for assessing *H. pylori* infection	Association	No. of asthmatic/ No. of control	Age	Quality
Bodner *et al*[3]	Serological	Seropositivity was similar in cases and controls	19/190	39-45	3/5
Tsang *et al*[22]	Serological	Seropositivity was similar in cases and controls	90/97	42.6 ± 16	2/5
Jun *et al*[14]	Serological	Seropositivity was similar in cases and controls (also for CagA)	46/48	51.2 ± 12.4	2/5
Chen *et al*[23]	Serological	*H. pylori*$^+$ CagA$^+$ were less likely to have ever been diagnosed as having asthma	525/7058	Adults	3/5
Chen *et al*[24]	Serological	Statistical significance only in age 3-13 yr	946/6466	⩾ 3	3/5
Reibma *et al*[25]	Serological	*H. pylori*$^+$ CagA$^+$ were less likely to have ever been diagnosed as having asthma	318/208	18-64	3/5
Shiotani *et al*[26]	Serological	Seropositivity was similar in cases and controls	6/771	New university students	2/3
Fullerton *et al*[27]	Serological	Seropositivity was similar in cases and controls	62/151	44.6 ± 13.5	3/5
Lim *et al*[28]	Serological	Statistical significance only in age < 40 yr	359/14673	18-91	3/5

H. pylori: *Helicobacter pylori*; CagA: Cytotoxin-associated gene A.

sample size: 526 participants, 318 cases, case-control study) (quality: 3/5) reported findings supporting data on the inverse association[25]. Only after adjustment for socio-economic status there was an inverse association between asthma and CagA$^+$ status (OR = 0.63, 95%CI: 0.41-0.98); (7) in a Japanese study[26] monocentric, sample size: 777 participants (6 cases), follow-up: 12 mo, observational cross-sectional study (quality: 2/5), newly enrolled university students with bronchial asthma, 24-year-old or younger, were all *H. pylori* negative; (8) no association between *H. pylori* seropositivity and asthma was found in an United Kingdom monocentric, sample size: 213 participants (62 cases), follow-up: 108 mo, cross-sectional study (quality 3/5) (OR = 1.09, 95%CI: 0.77-1.54)[27]; and (9) a monocentric, retrospective Korean study[28] (quality 3/5) enrolled subjects aged ⩾ 18 years who had health surveillance checkups, including the serum anti-*H. pylori* IgG level. This large scale study demonstrated an inverse relationship between *H. pylori* infection and asthma among adults < 40 years old.

Meta-analysis

In seven of the fourteen studies[3,14,17,19,20,24,25] has been reported both the prevalence of *H. pylori* infection in the asthma population and in the control population. There is heterogeneity between the studies (Cohran's Q = 0.02). The prevalence of *H. pylori* infection in the asthma population resulted 33.6% (518 of 1542), while the prevalence of *H. pylori* infection in the control population resulted 37.6% (2746 of 7310) (relative risk of *H. pylori* infection in the asthma population = 0.87, 95%CI: 0.72-1.05, *P* = 0.15, random effects model), difference not statistically significant. The forest plot is illustrated in Figure 1.

DISCUSSION

Potential pathogenetic mechanisms

In animal models, experimental infection with *H. pylori* during the neonatal period induced a protective effect against asthma[29].

In case of gastric colonization by *H. pylori*-CagA$^+$ strains, mucosal Tregs are higher in number, and mucosal levels of the immunomodulatory cytokine IL-10 may be higher compared to the case of colonization by *H. pylori*-CagA$^-$ strains[30-38].

Gastroesophageal reflux disease (GERD) could by a trigger to asthma symptoms[39]. Microaspiration of the gastric contents into the lung damages the bronchial mucosa, which results in mucosal inflammation and bronchial hyper-responsiveness. Diffuse gastric atrophy, a consequence of *H. pylori* infection, especially CagA$^+$ strains, is a protective factor against GERD[40]. Part of the lower prevalence of asthma in people affected by *H. pylori* infection could be justified by the lower prevalence of GERD in this patients and not by an immunologic shift to an Th2 phenotype.

Considering the available studies on the potential association between *H. pylori* and asthma, sources of heterogeneity can be identified.

Focusing on sample size, negative results obtained in the various studies, when a limited number of patients was examined, must be considered with caution for the possible risk of statistical ß error[41]. Another critical issue, on this matter, is represented by the fact that included populations are heterogeneous and this may have important repercussions: The differences observed could be due to an inadequate selection of the control group.

Methods for assessing *H. pylori* infection vary in sensitivity and specificity, which may result in misclassification of exposure to the bacteria. Focusing on methodologies employed, some may indicate a previous contact with the microorganism (serological tests) while others an infection under way (UBT, histology). Both kinds are useful when studying long-term processes in which the microorganism could have been the primum movens and its disappearance does not change the illness story. On the contrary, if its role in an acute attack is studied, it is more appropriate to search for the active infection.

In summary, in our meta-analysis a sample of 8852

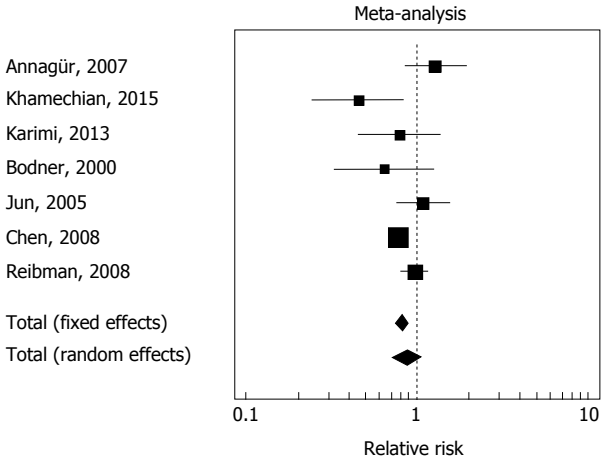

Figure 1 Relative risk of *Helicobacter pylori* population in the asthma population.

subjects are included and the prevalence of *H. pylori* infection in the asthma population resulted not statistically significant lower than in control population (relative risk = 0.87, P = 0.15).

The potential association between *H. pylori* infection and the reduction of risk of asthma development is an important issue in medicine, since it could influence the choice of bacterial treatment. The presence of *H. pylori* might be beneficial in childhood (decreasing risk of allergic diseases) but more deleterious later in life (increasing the risk of gastric adenocarcinoma).

Further prospective longitudinal studies with UBT for diagnosis of *H. pylori* are needed to prove a link between the lower prevalence of *H. pylori* infection and higher incidence of asthma.

COMMENTS

Background

Asthma is a common respiratory disease, manifested by inflammatory and obstructive processes, secondary to multiple stimuli. The etiology of asthma remains largely unclear. *Helicobacter pylori* (*H. pylori*) infection is a chronic one, generally acquired during childhood, and associated with lower socio-economic status.

Research frontiers

In the latest two decades, several studies have reported potential links between chronic *H. pylori* infection and a variety of extragastric manifestations. These include ischemic heart disease, liver diseases, skin diseases, rheumatic diseases, blood disorders, and others.

Innovations and breakthroughs

The present review attempts to highlight the data regarding a potential correlation between *H. pylori* infection and asthma.

Applications

The potential association between *H. pylori* infection and the reduction of risk of asthma development is an important issue in medicine, since it could influence the choice of bacterial treatment.

Peer-review

This is a well written meta-analysis paper concerning the elucidation of a potential involvement of *H. pylori* infection in the pathogenesis of asthma based on analysis of 14 papers selected from 169 publications.

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